PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 07 March 2001 (07.03.01)	
International application No. PCT/EP00/06215	**Applicant's or agent's file reference** 1999/121 WO
International filing date (day/month/year) 04 July 2000 (04.07.00)	**Priority date** (day/month/year) 22 July 1999 (22.07.99)
Applicant BERTHOLD, Achim et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

11 January 2001 (11.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Claudio Borton
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

EP0006215

PATENT COOPERATION TREATY

"Laidipin II", 99 17290

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
SCHMIDT, Werner
LTS Lohmann Therapie-Systeme AG
Postfach 1525
D-56605 Andernach
ALLEMAGNE

EINGANG LTS-PAT
12. Feb. 2001
ca. 4/1.

Date of mailing (day/month/year) 01 February 2001 (01.02.01)	
Applicant's or agent's file reference 1999/121 WO	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP00/06215	04 July 2000 (04.07.00)	22 July 1999 (22.07.99)

Applicant
LTS LOHMANN THERAPIE-SYSTEME AG et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   BR,CA,CN,CZ,EP,HU,IL,IN,JP,MX,NZ,PL,RU,TR,ZA

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   01 February 2001 (01.02.01) under No. WO 01/07017

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Continuation of Form PCT/IB/308

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year)	IMPORTANT NOTICE
01 February 2001 (01.02.01)	
Applicant's or agent's file reference	**International application No.**
1999/121 WO	PCT/EP00/06215

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

PATENT COOPERATION TREATY

"Lacidipin II"

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SCHMIDT, Werner
LTS LOHMANN THERAPIE-SYSTEME AG
Postfach 1525
56605 Andernach
ALLEMAGNE

EINGANG LTS-PAT
25. Sep. 2001

WV m.A.

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	24.09.2001
Applicant's or agent's file reference 1999/121 WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06215	04/07/2000	22/07/1999

Applicant
LTS LOHMANN THERAPIE-SYSTEME AG et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Longo, E Tel.+49 89 2399-8141

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1999/121 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06215	04/07/2000	22/07/1999
International Patent Classification (IPC) or national classification and IPC A61K9/70		
Applicant LTS LOHMANN THERAPIE-SYSTEME AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11/01/2001	24.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Muller, I Telephone No. +49 89 2399 8716

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06215

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

2-8	as originally filed			
1,1a	as received on	01/09/2001	with letter of	29/08/2001

Claims, No.:

1-12	as received on	01/09/2001	with letter of	29/08/2001

Drawings, sheets:

1/2,2/2	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 9,12, concerning industrial applicability.

because:

   ☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9,11,12
	No:	Claims	10
Inventive step (IS)	Yes:	Claims	1-9,11,12
	No:	Claims	10
Industrial applicability (IA)	Yes:	Claims	1-8,10,11
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Claims 9 and 12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

1. The amendments filed with letter dated 29.08.2001 are considered satisfying the requirement of Article 34 2)b) PCT.

2. Reference is made to the following documents:
D1: US-A-4 983 395 (THERA_TECH INC.) 8 January 1991 (1991-01-08) & 'Martindale 32th edition' , PHARMACEUTICAL PRESS , LONDON
D2: US-A-4 956 171 (CHANG YUNIK) 11 September 1990 (1990-09-11) & 'Martindale 32th edition' , PHARMACEUTICAL PRESS , LONDON
D3: EP-A-0 680 759 (RHODE ISLAND EDUCATION) 8 November 1995 (1995-11-08) & 'Martindale 32th edition' , PHARMACEUTICAL PRESS , LONDON
D4: SHIRAKURA O; OHSHIMA A; TSUNEMI S: 'Synergistic effect of D-Limonene and ethanol on the transdermal penetration of NB-818' DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, vol. 21, no. 4, 1995, pages 411-425, XP000961163.

3. Novelty (Article 33(2) PCT)

3.1 The subject-matter of the independent claim 1, and hence, of claims 2-7 depending thereon, meets the requirement of novelty vis-à-vis the prior art D1-D4 cited in the international search report:
None of these documents discloses a transdermal therapeutic system for administering a calcium antagonist of the dihydropyridine type, which drug reservoir contains a solution comprising a combination of the calcium antagonist, a pyrrolidone derivative and both an alcohol and a fatty acid ester such as defined in present claim 1.

3.2 The transdermal therapeutic system of claim 1 meeting the requirement of novelty, the use of said calcium antagonist in the manufacture of said transdermal therapeutic system, defined in present independent claim 8, also meets the requirement of novelty.

3.3 The same as afore-mentioned applies to the method for administering a calcium antagonist as defined in present independent claims 9 and 12.

3.4 In view of the lack of clarity of present independent claim 10 (cf. item VIII, 1.), the subject-matter of this claim, interpreted in its broadest meaning, merely defines a solution which is **suitable** for use in a transdermal therapeutic system../... From the structure of claim 10, the technical features of the particular constituents of the solution in the drug reservoir are considered as being part of the subject-matter of claims 1-7 and cannot be considered for delimitation of the solution as such from the prior art. Consequently, a solution as presently defined in claim 10 can solely consist of for example ethanol or water, both of which are suitable for use in said transdermal delivery devices.
Hence, the subject-matter of claim 10 lacks novelty over the prior art.

However, dependent claim 11, defining as constituents of the claimed solution the calcium antagonist, ethanol, N-methyl-2-pyrrolidinone and sorbitan palmitate is considered novel over the state of the art cited in the international search report, of which none discloses such solution for use in transdermal delivery systems.

4. Inventive Step (Article 33(3) PCT)

4.1 In view of the technical problem to be solved (providing a transdermal therapeutic system (claims 1-7), the use of a calcium antagonist for the manufacture of such system (claim 8) and a method of administration of a calcium antagonist from such system (claims 9 and 12) for effective delivery of a calcium antagonist of the dihydropyridine type) and its non-obvious solution (combining in the drug reservoir the calcium antagonist with as skin permeation enhancer, respectively solvent, a pyrrolidone derivative, saturated or unsaturated fatty acid ester of a carboxylic acid containing 8-16 carbon atoms and a polyhydroxy alcohol, and an alcohol such defined in present claim 1), the subject-matter of the claims 1-7, 8, 9 and 12

is considered meeting the requirement of Article 33(3) PCT.

4.2 The same as stated above is considered applying for the solution defined in the dependent claim 11, referring to claim 10, none of the state of the art documents cited providing neither suggestion, nor hint for combining such constituents in a solution suitable for use in a transdermal therapeutic system according to the claims 1 to 7.
Hence, claim 11 appears to satisfy the requirement of Art. 33(3) PCT.

5. Industrial Applicability (Article 33(4) PCT)

5.1 For the assessment of the present claims 9 and 12 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5.2 The subject-matter of the claims 1-8, 10 and 11 is applicable in the pharmaceutic industry.

Re Item VIII (Art. 6 PCT)

1. Claim 10 directed to a solution is rendered unclear by defining as technical feature a feature (transdermal therapeutic system as claimed in any of claims 1 to 7 which comprises a calcium antagonist etc.) which is in fact part of the independent claim 1 to which reference is made (solution which is suitable for use in a transdermal therapeutic system as claimed in any of claims 1 to 7).
2. Lack of support of the claims arises by defining in the description at page 6, third paragraph as subject-matter of the invention a process for the production of transdermal therapeutic systems, not forming part of the claims.

Pharmaceutical composition

Description

The present invention relates to a transdermal therapeutic system for the therapeutic administration of calcium antagonists of the dihydropyridine type, to a process for its preparation and to its use in medicine.

Calcium antagonists of the dihydropyridine type are compounds which influence the inflow of calcium ions into cells in particular into the cells of smooth muscles. Such compounds of the dihydropyridine type have been described, for example, in U.S. patent 3,799,934, U.S. patent 3,644,627, U.S. patent 4,264,611, and U.S. patent 4,801,599, which patents are incorporated by reference.

Calcium antagonists of the dihydropyridine type include, for example (without in any way limiting the scope of the invention), amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, and nitrendipine.

Diethyl (E)-4-[2-[(tert-butylcarbonyl)vinyl]phenyl-1,4-dihydro-2,6-dimethylpyridine-3,5 dicarboxylate (Lacidipine) is one of the preferred compounds of the dihydropyridine type. Lacidipine, which is described in British patent No. 2164336, is a potent long acting calcium antagonist which is particularly useful for treating hypertension. The compound may also be useful for the treatment of other cardiovascular disorders including atherosclerosis, peripheral vascular disease, ischaemic heart disease and congestive heart failure.

Nifedipine, which is described in U.S. patent 3,644,627, is another preferred calcium antagonists of the dihydropyridine type.

U.S. patent 4,983,395 pertains to transdermal drug delivery devices wherein the reservoir may comprise a gel consisting of nicardipine-hydrochloride, ® Klucel HF and a mixture of ethanol, water, glycerol and glycerol monooleate.

Transdermal drug delivery devices for co-administration of a drug such as nifedipine and a dual permeation enhancer comprising sucrose cocoate and methyl laurate are known from U.S. patent 4,956,171. The reservoir can contain nifedipine in methyl laurate or an aqueous solution of sucrose cocoate or in combination thereof.

EP-A 680,759 pertains to transdermal formulations of DHP calcium antagonists in a mixed liquid comprising cis-oleic acid and dimethylisosorbide dispersed in a propylene glycol base.

The promoting effect of a combination of limonene and ethanol has been found in Shirakura et al., Drug Development and Industrial Pharmacy, Vol. 21, No.4, 1995, pages 411 – 425 to synergistically enhance the transdermal adsorption of the DHP calcium antagonist NB-818.

Transdermal drug delivery systems provide a means for obtaining a high degree of control of drug concentration in the blood over a specified time period. Many systems have been developed and used to deliver drugs transdermally. It is however widely recognised that in general it is not possible to predict which particular systems will

New Claims

1. A transdermal therapeutic system for administering a calcium antagonist of the dihydropyridine type which comprises
   (a) a backing layer, which defines the upper surface of the device,
   (b) a drug reservoir containing a solution comprising
      - a calcium antagonist of the dihydropyridine type,
      - an alcohol selected from the group consisting of ethanol, propanol, isopropanol and n-decyl alcohol,
      - a pyrrolidone derivative, and
      - a saturated or unsaturated fatty acid ester of a carboxylic acid containing 8 – 16 carbon atoms and a polyhydroxy alcohol,
   (c) a membrane to control the release of the active ingredient, and
   (d) a pressure sensitive adhesive layer for attaching the system to the skin and, if necessary, a release liner on the outer face of the adhesive layer wherein the said backing layer and said membrane are connected together to form the drug reservoir.

2. A transdermal therapeutic system as claimed in claim 1 wherein the solution in the drug reservoir comprises a calcium antagonist of the dihydropyridine type, ethanol, N-methyl-2-pyrrolidinone and sorbitan palminate.

3. A transdermal therapeutic system as claimed in claim 2 wherein the solution comprises a calcium antagonist of the dihydropyridine type 3 - 5 %, ethanol 30 - 40 %, sorbitan palmitate 3 - 5 % and N-methyl-2-pyrrolidinone 50 - 60 % by weight of the total solution.

4. A transdermal therapeutic system as claimed in any of claims 1 to 3 in the form of skin patch.

5. A transdermal therapeutic system as claimed in any of claims 1 to 4 in which the calcium antagonist of the dihydropyridine type is selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, and nitrendipine.

6. A transdermal therapeutic system as claimed in any of claims 1 to 5 in which the calcium antagonist of the dihydropyridine type is lacidipine.

7. A transdermal therapeutic system as claimed in any of claims 1 to 5 in which the calcium antagonist of the dihydropyridine type is nifedipine.

8. The use of a calcium antagonist of the dihydropyridine type for the manufacture of a transdermal therapeutic system as claimed in any of claims 1 to 7 for administration of a calcium antagonist of the dihydropyridine type through a pre-determined area of intact skin for the treatment of cardiovascular disorders including hypertension.

9. A method for administering a calcium antagonist of the dihydropyridine type through a pre-determined area of intact skin and at an administration rate such as to reach and maintain an effective therapeutic dose of a calcium antagonist of the dihydropyridine type for the control of hypertension and other cardiovascular diseases which comprises applying to the skin a transdermal therapeutic system as claimed in any of claims 1 to 7.

10. A solution which is suitable for use in a transdermal therapeutic system as claimed in any of claims 1 to 7 which comprises
a drug reservoir containing a solution comprising
- a calcium antagonist of the dihydropyridine type,
- an alcohol selected from the group consisting of ethanol, propanol, isopropanol and n-decyl alcohol,
- a pyrrolidone derivative, and
- a saturated or unsaturated fatty acid ester of a carboxylic acid containing 8 – 16 carbon atoms and a polyhydroxy alcohol.

11. A solution as claimed in claim 10 which comprises a calcium antagonist of the dihydropyridine type, ethanol, N-methyl-2-pyrrolidinone and sorbitan palmitate.

12. A method of treating hypertension which comprises administering an effective amount of a calcium antagonist of the dihydropyridine type in a transdermal therapeutic system as claimed in any of claims 1 to 7.

PCT

ANTRAG

Der Unterzeichnete beantragt, daß die vorliegende internationale Anmeldung nach dem Vertrag über die internationale Zusammenarbeit auf dem Gebiet des Patentwesens behandelt wird.

Vom Anmeldeamt auszufüllen

Internationales Aktenzeichen

Internationales Anmeldedatum

Name des Anmeldeamts und "PCT International Application"

Aktenzeichen des Anmelders oder Anwalts *(falls gewünscht)* *(max. 12 Zeichen)* 1999/121 WO

Feld Nr. I BEZEICHNUNG DER ERFINDUNG

Pharmaceutical composition

Feld Nr. II ANMELDER

Name und Anschrift: *(Familienname, Vorname; bei juristischen Personen vollständige amtliche Bezeichnung. Bei der Anschrift sind die Postleitzahl und der Name des Staats anzugeben. Der in diesem Feld in der Anschrift angegebene Staat ist der Staat des Sitzes oder Wohnsitzes des Anmelders, sofern nachstehend kein Staat des Sitzes oder Wohnsitzes angegeben ist.)*

LTS Lohmann Therapie-Systeme AG
Lohmannstraße 2
D-56626 Andernach
DE

☐ Diese Person ist gleichzeitig Erfinder

Telefonnr.: 02632/992362

Telefaxnr.: 02632/992387

Fernschreibnr.:

Staatsangehörigkeit (Staat): DE

Sitz oder Wohnsitz (Staat): DE

Diese Person ist Anmelder für folgende Staaten: ☐ alle Bestimmungsstaaten ☒ alle Bestimmungsstaaten mit Ausnahme der Vereinigten Staaten von Amerika ☐ nur die Vereinigten Staaten von Amerika ☐ die im Zusatzfeld angegebenen Staaten

Feld Nr. III WEITERE ANMELDER UND/ODER (WEITERE) ERFINDER

Name und Anschrift: *(Familienname, Vorname; bei juristischen Personen vollständige amtliche Bezeichnung. Bei der Anschrift sind die Postleitzahl und der Name des Staats anzugeben. Der in diesem Feld in der Anschrift angegebene Staat ist der Staat des Sitzes oder Wohnsitzes des Anmelders, sofern nachstehend kein Staat des Sitzes oder Wohnsitzes angegeben ist.)*

Berthold, Achim
Erfurter Strasse 1
D-56626 Andernach
DE

Diese Person ist:

☐ nur Anmelder

☒ Anmelder und Erfinder

☐ nur Erfinder *(Wird dieses Kästchen angekreuzt, so sind die nachstehenden Angaben nicht nötig.)*

Staatsangehörigkeit (Staat): DE

Sitz oder Wohnsitz (Staat): DE

Diese Person ist Anmelder für folgende Staaten: ☐ alle Bestimmungsstaaten ☐ alle Bestimmungsstaaten mit Ausnahme der Vereinigten Staaten von Amerika ☒ nur die Vereinigten Staaten von Amerika ☐ die im Zusatzfeld angegebenen Staaten

☒ Weitere Anmelder und/oder (weitere) Erfinder sind auf einem Fortsetzungsblatt angegeben.

Feld Nr. IV ANWALT ODER GEMEINSAMER VERTRETER; ODER ZUSTELLANSCHRIFT

Die folgende Person wird hiermit bestellt/ist bestellt worden, um für den (die) Anmelder vor den zuständigen internationalen Behörden in folgender Eigenschaft zu handeln als: ☒ Anwalt ☐ gemeinsamer Vertreter

Name und Anschrift: *(Familienname, Vorname; bei juristischen Personen vollständige amtliche Bezeichnung. Bei der Anschrift sind die Postleitzahl und der Name des Staats anzugeben.)*

Schmidt, Werner
LTS Lohmann Therapie-Systeme AG
Postfach 1525
D-56605 Andernach
DE

Telefonnr.: 02362/992362

Telefaxnr.: 02632/992387

Fernschreibnr.:

☐ **Zustellanschrift:** Dieses Kästchen ist anzukreuzen, wenn kein Anwalt oder gemeinsamer Vertreter bestellt ist und statt dessen im obigen Feld eine spezielle Zustellanschrift angegeben ist.

Fortsetzung von Feld Nr. III WEITERE ANMELDER UND/ODER (WEITERE) ERFINDER

Wird keines der folgenden Felder benutzt, so sollte dieses Blatt dem Antrag nicht beigefügt werden.

Name und Anschrift: *(Familienname, Vorname; bei juristischen Personen vollständige amtliche Bezeichnung. Bei der Anschrift sind die Postleitzahl und der Name des Staats anzugeben. Der in diesem Feld in der Anschrift angegebene Staat ist der Staat des Sitzes oder Wohnsitzes des Anmelders, sofern nachstehend kein Staat des Sitzes oder Wohnsitzes angegeben ist.)*

Müller, Walter
Engerser Strasse 56
D-56564 Neuwied
DE

Diese Person ist:
- ☐ nur Anmelder
- ☒ Anmelder und Erfinder
- ☐ nur Erfinder *(Wird dieses Kästchen angekreuzt, so sind die nachstehenden Angaben nicht nötig.)*

Staatsangehörigkeit (Staat): DE

Sitz oder Wohnsitz (Staat): DE

Diese Person ist Anmelder für folgende Staaten: ☐ alle Bestimmungsstaaten ☐ alle Bestimmungsstaaten mit Ausnahme der Vereinigten Staaten von Amerika ☒ nur die Vereinigten Staaten von Amerika ☐ die im Zusatzfeld angegebenen Staaten

Name und Anschrift: *(Familienname, Vorname; bei juristischen Personen vollständige amtliche Bezeichnung. Bei der Anschrift sind die Postleitzahl und der Name des Staats anzugeben. Der in diesem Feld in der Anschrift angegebene Staat ist der Staat des Sitzes oder Wohnsitzes des Anmelders, sofern nachstehend kein Staat des Sitzes oder Wohnsitzes angegeben ist.)*

Gaviraghi, Giovanni
Glaxo Wellcome S.p.A.
Via A. Fleming 2
I-37100 Verona
IT

Diese Person ist:
- ☐ nur Anmelder
- ☒ Anmelder und Erfinder
- ☐ nur Erfinder *(Wird dieses Kästchen angekreuzt, so sind die nachstehenden Angaben nicht nötig.)*

Staatsangehörigkeit (Staat): IT

Sitz oder Wohnsitz (Staat): IT

Diese Person ist Anmelder für folgende Staaten: ☐ alle Bestimmungsstaaten ☐ alle Bestimmungsstaaten mit Ausnahme der Vereinigten Staaten von Amerika ☒ nur die Vereinigten Staaten von Amerika ☐ die im Zusatzfeld angegebenen Staaten

Name und Anschrift: *(Familienname, Vorname; bei juristischen Personen vollständige amtliche Bezeichnung. Bei der Anschrift sind die Postleitzahl und der Name des Staats anzugeben. Der in diesem Feld in der Anschrift angegebene Staat ist der Staat des Sitzes oder Wohnsitzes des Anmelders, sofern nachstehend kein Staat des Sitzes oder Wohnsitzes angegeben ist.)*

Diese Person ist:
- ☐ nur Anmelder
- ☐ Anmelder und Erfinder
- ☐ nur Erfinder *(Wird dieses Kästchen angekreuzt, so sind die nachstehenden Angaben nicht nötig.)*

Staatsangehörigkeit (Staat):

Sitz oder Wohnsitz (Staat):

Diese Person ist Anmelder für folgende Staaten: ☐ alle Bestimmungsstaaten ☐ alle Bestimmungsstaaten mit Ausnahme der Vereinigten Staaten von Amerika ☐ nur die Vereinigten Staaten von Amerika ☐ die im Zusatzfeld angegebenen Staaten

Name und Anschrift: *(Familienname, Vorname; bei juristischen Personen vollständige amtliche Bezeichnung. Bei der Anschrift sind die Postleitzahl und der Name des Staats anzugeben. Der in diesem Feld in der Anschrift angegebene Staat ist der Staat des Sitzes oder Wohnsitzes des Anmelders, sofern nachstehend kein Staat des Sitzes oder Wohnsitzes angegeben ist.)*

Diese Person ist:
- ☐ nur Anmelder
- ☐ Anmelder und Erfinder
- ☐ nur Erfinder *(Wird dieses Kästchen angekreuzt, so sind die nachstehenden Angaben nicht nötig.)*

Staatsangehörigkeit (Staat):

Sitz oder Wohnsitz (Staat):

Diese Person ist Anmelder für folgende Staaten: ☐ alle Bestimmungsstaaten ☐ alle Bestimmungsstaaten mit Ausnahme der Vereinigten Staaten von Amerika ☐ nur die Vereinigten Staaten von Amerika ☐ die im Zusatzfeld angegebenen Staaten

☐ Weitere Anmelder und/oder (weitere) Erfinder sind auf einem zusätzlichen Fortsetzungsblatt angegeben.

Feld Nr. V BESTIMMUNG VON STAATEN

Die folgenden Bestimmungen nach Regel 4.9 Absatz a werden hiermit vorgenommen *(bitte die entsprechenden Kästchen ankreuzen; wenigstens ein Kästchen muß angekreuzt werden)*:

Regionales Patent

☐ AP **ARIPO-Patent:** GH Ghana, GM Gambia, KE Kenia, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swasiland, TZ Vereinigte Republik Tansania, UG Uganda, ZW Simbabwe und jeder weitere Staat, der Vertragsstaat des Harare-Protokolls und des PCT ist

☐ EA **Eurasisches Patent:** AM Armenien, AZ Aserbaidschan, BY Belarus, KG Kirgisistan, KZ Kasachstan, MD Republik Moldau, RU Russische Föderation, TJ Tadschikistan, TM Turkmenistan und jeder weitere Staat, der Vertragsstaat des Eurasischen Patentübereinkommens und des PCT ist

☒ EP **Europäisches Patent:** AT Österreich, BE Belgien, CH und LI Schweiz und Liechtenstein, CY Zypern, DE Deutschland, DK Dänemark, ES Spanien, FI Finnland, FR Frankreich, GB Vereinigtes Königreich, GR Griechenland, IE Irland, IT Italien, LU Luxemburg, MC Monaco, NL Niederlande, PT Portugal, SE Schweden und jeder weitere Staat, der Vertragsstaat des Europäischen Patentübereinkommens und des PCT ist

☐ OA **OAPI-Patent:** BF Burkina Faso, BJ Benin, CF Zentralafrikanische Republik, CG Kongo, CI Côte d'Ivoire, CM Kamerun, GA Gabun, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauretanien, NE Niger, SN Senegal, TD Tschad, TG Togo und jeder weitere Staat, der Vertragsstaat der OAPI und des PCT ist *(falls eine andere Schutzrechtsart oder ein sonstiges Verfahren gewünscht wird, bitte auf der gepunkteten Linie angeben)* .....

Nationales Patent *(falls eine andere Schutzrechtsart oder ein sonstiges Verfahren gewünscht wird, bitte auf der gepunkteten Linie angeben)*:

☐ AE Vereinigte Arabische Emirate
☐ AL Albanien
☐ AM Armenien
☐ AT Österreich
☒ AU Australien
☐ AZ Aserbaidschan
☐ BA Bosnien-Herzegowina
☐ BB Barbados
☐ BG Bulgarien
☒ BR Brasilien
☐ BY Belarus
☒ CA Kanada
☐ CH und LI Schweiz und Liechtenstein
☒ CN China
☐ CR Costa Rica
☐ CU Kuba
☒ CZ Tschechische Republik
☐ DE Deutschland
☐ DK Dänemark
☐ DM Dominica
☐ EE Estland
☐ ES Spanien
☐ FI Finnland
☐ GB Vereinigtes Königreich
☐ GD Grenada
☐ GE Georgien
☐ GH Ghana
☐ GM Gambia
☐ HR Kroatien
☒ HU Ungarn
☐ ID Indonesien
☒ IL Israel
☒ IN Indien
☐ IS Island
☒ JP Japan
☐ KE Kenia
☐ KG Kirgisistan
☐ KP Demokratische Volksrepublik Korea
☒ KR Republik Korea
☐ KZ Kasachstan
☐ LC Saint Lucia
☐ LK Sri Lanka
☐ LR Liberia
☐ LS Lesotho
☐ LT Litauen
☐ LU Luxemburg
☐ LV Lettland
☐ MA Marokko
☐ MD Republik Moldau
☐ MG Madagaskar
☐ MK Die ehemalige jugoslawische Republik Mazedonien
☐ MN Mongolei
☐ MW Malawi
☒ MX Mexiko
☐ NO Norwegen
☒ NZ Neuseeland
☒ PL Polen
☐ PT Portugal
☐ RO Rumänien
☒ RU Russische Föderation
☐ SD Sudan
☐ SE Schweden
☐ SG Singapur
☐ SI Slowenien
☐ SK Slowakei
☐ SL Sierra Leone
☐ TJ Tadschikistan
☐ TM Turkmenistan
☒ TR Türkei
☐ TT Trinidad und Tobago
☐ TZ Vereinigte Republik Tansania
☐ UA Ukraine
☐ UG Uganda
☒ US Vereinigte Staaten von Amerika
☐ UZ Usbekistan
☐ VN Vietnam
☐ YU Jugoslawien
☒ ZA Südafrika
☐ ZW Simbabwe

Kästchen für die Bestimmung von Staaten, die dem PCT nach der Veröffentlichung dieses Formblatts beigetreten sind:

☐ .....
☐ .....

Erklärung bzgl. vorsorglicher Bestimmungen: Zusätzlich zu den oben genannten Bestimmungen nimmt der Anmelder nach Regel 4.9 Absatz b auch alle anderen nach dem PCT zulässigen Bestimmungen vor mit Ausnahme der im Zusatzfeld genannten Bestimmungen, die von dieser Erklärung ausgenommen sind. Der Anmelder erklärt, daß diese zusätzlichen Bestimmungen unter dem Vorbehalt einer Bestätigung stehen und jede zusätzliche Bestimmung, die vor Ablauf von 15 Monaten ab dem Prioritätsdatum nicht bestätigt wurde, nach Ablauf dieser Frist als vom Anmelder zurückgenommen gilt. *(Die Bestätigung (einschließlich der Gebühren) muß beim Anmeldeamt innerhalb der Frist von 15 Monaten eingehen.)*

Feld Nr. VI PRIORITÄTSANSPRUCH ☐ Weitere Prioritätsansprüche sind im Zusatzfeld angegeben.

Anmeldedatum der früheren Anmeldung (Tag Monat, Jahr)	Aktenzeichen der früheren Anmeldung	Ist die frühere Anmeldung eine: nationale Anmeldung: Staat	regionale Anmeldung:* regionales Amt	internationale Anmeldung Anmeldeamt
Zeile (1) 22. Juli 1999 (22.07.1999)	9917290.0	GB		
Zeile (2)				
Zeile (3)				

☐ Das Anmeldeamt wird ersucht, eine beglaubigte Abschrift der oben in der (den) Zeile(n) _____ bezeichneten früheren Anmeldung(en) zu erstellen und dem internationalen Büro zu übermitteln *(nur falls die frühere Anmeldung(en) bei dem Amt eingereicht worden ist(sind), das für die Zwecke dieser internationalen Anmeldung Anmeldeamt ist)*

* *Falls es sich bei der früheren Anmeldung um eine ARIPO-Anmeldung handelt, so muß in dem Zusatzfeld mindestens ein Staat angegeben werden, der Mitgliedstaat der Pariser Verbandsübereinkunft zum Schutz des gewerblichen Eigentums ist und für den die frühere Anmeldung eingereicht wurde.*

Feld Nr. VII INTERNATIONALE RECHERCHENBEHÖRDE

Wahl der internationalen Recherchenbehörde (ISA) *(falls zwei oder mehr als zwei internationale Recherchenbehörden für die Ausführung der internationalen Recherche zuständig sind, geben Sie die von Ihnen gewählte Behörde an; der Zweibuchstaben-Code kann benutzt werden):*

ISA /

Antrag auf Nutzung der Ergebnisse einer früheren Recherche; Bezugnahme auf diese frühere Recherche *(falls eine frühere Recherche bei der internationalen Recherchenbehörde beantragt oder von ihr durchgeführt worden ist):*

Datum *(Tag/Monat/Jahr)* Aktenzeichen Staat *(oder regionales Amt)*

Feld Nr. VIII KONTROLLISTE; EINREICHUNGSSPRACHE

Diese internationale Anmeldung enthält die folgende **Anzahl von Blättern:**

Antrag	: 4
Beschreibung (ohne Sequenzprotokollteil)	: 8
Ansprüche	: 2
Zusammenfassung	: 1
Zeichnungen	: 2
Sequenzprotokollteil der Beschreibung	:
Blattzahl insgesamt	: 17

Dieser internationalen Anmeldung **liegen** die nachstehend angekreuzten Unterlagen **bei:**

1. ☒ Blatt für die Gebührenberechnung
2. ☐ Gesonderte unterzeichnete Vollmacht
3. ☒ Kopie der allgemeinen Vollmacht; Aktenzeichen (falls vorhanden): 40874
4. ☐ Begründung für das Fehlen einer Unterschrift
5. ☐ Prioritätsbeleg(e), in Feld Nr. VI durch folgende Zeilennummer gekennzeichnet:
6. ☐ Übersetzung der internationalen Anmeldung in die folgende Sprache:
7. ☐ Gesonderte Angaben zu hinterlegten Mikroorganismen oder anderem biologischen Material
8. ☐ Protokoll der Nucleotid- und/oder Aminosäuresequenzen in computerlesbarer Form
9. ☐ Sonstige *(einzeln aufführen):*

Abbildung der Zeichnungen, die mit der Zusammenfassung veröffentlicht werden soll (Nr.): 1

Sprache, in der die internationale Anmeldung eingereicht wird: deutsch

Feld Nr. IX UNTERSCHRIFT DES ANMELDERS ODER DES ANWALTS

Der Name jeder unterzeichnenden Person ist neben der Unterschrift zu wiederholen, und es ist anzugeben, sofern sich dies nicht eindeutig aus dem Antrag ergibt, in welcher Eigenschaft die Person unterzeichnet.

W. Schmidt ..... Schmidt, Werner ..... Gaviraghi, Giovanni

..... Berthold, Achim

..... Müller, Walter

Vom Anmeldeamt auszufüllen

1. Datum des tatsächlichen Eingangs dieser internationalen Anmeldung:
2. Zeichnungen ☐ eingegangen: ☐ nicht eingegangen:
3. Geändertes Eingangsdatum aufgrund nachträglich, jedoch fristgerecht eingegangener Unterlagen oder Zeichnungen zur Vervollständigung dieser internationalen Anmeldung:
4. Datum des fristgerechten Eingangs der angeforderten Richtigstellungen nach Artikel 11(2) PCT:
5. Internationale Recherchenbehörde *(falls zwei oder mehr zuständig sind)*: ISA /
6. ☐ Übermittlung des Recherchenexemplars bis zur Zahlung der Recherchengebühr aufgeschoben

Vom Internationalen Büro auszufüllen

Datum des Eingangs des Aktenexemplars beim Internationalen Büro:

Dieses Blatt ist nicht Teil und zählt nicht als Blatt der internationalen Anmeldung.

PCT

BLATT FÜR DIE GEBÜHRENBERECHNUNG

Anhang zum Antrag

Von Anmeldeamt auszufüllen

Internationales Aktenzeichen

Eingangsstempel des Anmeldeamts

Aktenzeichen des Anmelders oder Anwalts 1999/121 WO

Anmelder
LTS Lohmann Therapie-Systeme AG

BERECHNUNG DER VORGESCHRIEBENEN GEBÜHREN

1. ÜBERMITTLUNGSGEBÜHR . . . . . € 102,-- T

2. RECHERCHENGEBÜHR . . . . . € 945,-- S

Die internationale Recherche ist durchzuführen von _____

(Sind zwei oder mehr Internationale Recherchenbehörden für die internationale Recherche zuständig, ist der Name der Behörde anzugeben, die die internationale Recherche durchführen soll.)

3. INTERNATIONALE GEBÜHR

Grundgebühr

Die internationale Anmeldung enthält 17 Blätter.

umfaßt die ersten 30 Blätter . . . . . € 409,-- b1

_____ (Anzahl der Blätter über 30) x € 9,-- (Zusatzblattgebühr) = _____ b2

Addieren Sie die in Feld b1 und b2 eingetragenen Beträge, und tragen Sie die Summe in Feld B ein . . . . € 409,-- B

Bestimmungsgebühren

Die internationale Anmeldung enthält 18 Bestimmungen.

8 (Anzahl der zu zahlenden Bestimmungsgebühren *(maximal 8)*) x € 88,-- (Bestimmungsgebühr) = € 704,-- D

Addieren Sie die in Feld B und D eingetragenen Beträge, und tragen Sie die Summe in Feld I ein . . . . . € 1113,-- I

(Anmelder aus einigen Staaten haben Anspruch auf eine Ermäßigung der internationalen Gebühr um 75%. Hat der Anmelder (oder haben alle Anmelder) einen solchen Anspruch, so beträgt der in Feld I einzutragende Gesamtbetrag 25% der Summe der in Feld B und D eingetragenen Beträge.)

4. GEBÜHR FÜR PRIORITÄTSBELEG *(ggf.)* . . . . . P

5. GESAMTBETRAG DER ZU ZAHLENDEN GEBÜHREN
Addieren Sie die in Feldern T, S, I und P eingetragenen Beträge, und tragen Sie die Summe in das nebenstehende Feld ein . . . . . € 2160,-- INSGESAMT

☐ Die Bestimmungsgebühren werden jetzt noch nicht gezahlt.

ZAHLUNGSWEISE

☐ Abbuchungsauftrag (siehe unten) ☐ Bankwechsel ☐ Kupons

☒ Scheck ☐ Barzahlung ☐ Sonstige *(einzeln angeben):*

☐ Postanweisung ☐ Gebührenmarken

ABBUCHUNGSAUFTRAG *(diese Zahlungsweise gibt es nicht bei allen Anmeldeämtern)*

Das Anmeldeamt/ _____

☐ wird beauftragt, den vorstehend angegebenen Gesamtbetrag der Gebühren von meinem laufenden Konto abzubuchen.

☐ *(dieses Kästchen darf nur angekreuzt werden, wenn die Vorschriften des Anmeldeamts über laufende Konten dieses Verfahren erlauben)* wird beauftragt, Fehlbeträge oder Überzahlungen des vorstehend angegebenen Gesamtbetrags der Gebühren meinem laufenden Konto zu belasten bzw. gutzuschreiben.

☐ wird beauftragt, die Gebühr für die Ausstellung des Prioritätsbelegs und seine Übermittlung an das Internationale Büro der WIPO von meinem laufenden Konto abzubuchen.

Kontonummer _____ Datum *(Tag/Monat/Jahr)* _____ Unterschrift _____

Siehe Anmerkungen zum Blatt für die Gebührenberechnung

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
1999/121 WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/06215	04/07/2000	22/07/1999
Applicant		
LTS LOHMANN THERAPIE-SYSTEME AG		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   TRANSDERMAL THERAPEUTIC SYSTEM FOR ADMINISTERING A CALCIUM ANTAGONIST

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 8 relates to an extremely large number of possible systems. In fact, the term "essentially" in the claim contains so many options that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear, namely claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Internat[redacted]Application No
PCT/[redacted]00/06215

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/70 A61K31/44 A61P9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 4 983 395 A (THERA_TECH INC.) 8 January 1991 (1991-01-08) column 3, line 17 -column 6, line 21 column 7, line 47 -column 8, line 2; example 3 claims 1-6	1,4,5, 8-11,14 13
A	& "Martindale 32th edition" , PHARMACEUTICAL PRESS , LONDON page 915, column 1 ---	9,10,14
X Y	US 4 956 171 A (CHANG YUNIK) 11 September 1990 (1990-09-11) column 3, line 14 - line 50 column 9; table 4 claims 1-6	1,4,5, 7-11,14 13
A	& "Martindale 32th edition" , PHARMACEUTICAL PRESS , LONDON page 919, column 3 --- -/--	9,10,14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 2000	11/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Muller, S

3

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X Y A	EP 0 680 759 A (RHODE ISLAND EDUCATION) 8 November 1995 (1995-11-08) page 6 -page 7; examples 3,4 claims 1-11 & "Martindale 32th edition" , PHARMACEUTICAL PRESS , LONDON page 919, column 3	1,4,5, 7-11,14 13 9,10,14
Y	SHIRAKURA O; OHSHIMA A; TSUNEMI S: "Synergistic effect of D-Limonene and ethanol on the transdermal penetration of NB-818" DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, vol. 21, no. 4, 1995, pages 411-425, XP000961163 abstract	13
T	WO 00 47208 A (SEO BO YOUN ;CHO JOONG WOONG (KR); HWANG JUN SEOK (KR); SAMYANG CO) 17 August 2000 (2000-08-17) page 3, line 22 - line 24 page 6, line 22 -page 9, line 14 claims 1,2,15	2,3,12

3

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat[redacted] Application No
PCT/EP 00/06215

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4983395 A	08-01-1991	US 4849224 A	18-07-1989
		AT 154751 T	15-07-1997
		AU 631417 B	26-11-1992
		AU 5341690 A	22-10-1990
		CA 2053272 A,C	22-09-1990
		DE 69030974 D	31-07-1997
		DE 69030974 T	18-12-1997
		DK 464106 T	21-07-1997
		EP 0464106 A	08-01-1992
		ES 2103271 T	16-09-1997
		HK 1003322 A	23-10-1998
		JP 8018976 B	28-02-1996
		JP 4506062 T	22-10-1992
		KR 149492 B	01-10-1998
		WO 9011065 A	04-10-1990
		AT 81023 T	15-10-1992
		AU 2467788 A	18-05-1989
		CA 1302824 A	09-06-1992
		DE 3875068 A	05-11-1992
		DE 3875068 T	15-04-1993
		EP 0316168 A	17-05-1989
		ES 2035928 T	01-05-1993
		GR 3006563 T	30-06-1993
		JP 1760026 C	20-05-1993
		JP 2001283 A	05-01-1990
		JP 4046592 B	30-07-1992
		KR 9301082 B	15-02-1993
US 4956171 A	11-09-1990	NONE	
EP 0680759 A	08-11-1995	NONE	
WO 0047208 A	17-08-2000	NONE	

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 February 2001 (01.02.2001)

PCT

(10) International Publication Number
WO 01/07017 A1

(51) International Patent Classification[7]: A61K 9/70, 31/44, A61P 9/14

(21) International Application Number: PCT/EP00/06215

(22) International Filing Date: 4 July 2000 (04.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9917290.0 22 July 1999 (22.07.1999) GB

(71) Applicant *(for all designated States except US)*: LTS LOHMANN THERAPIE-SYSTEME AG [DE/DE]; Lohmannstrasse 2, D-56626 Andernach (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BERTHOLD, Achim [DE/DE]; Erfurter Strasse 1, D-56626 Andernach (DE). MÜLLER, Walter [DE/DE]; Engerser Strasse 56, D-56564 Neuwied (DE). GAVIRAGHI, Giovanni [IT/IT]; Glaxo Wellcome S.p.A., Via A. Fleming, 2, I-37100 Verona (IT).

(74) Agent: SCHMIDT, Werner; LTS Lohmann Therapie-Systeme AG, Postfach 1525, D-56605 Andernach (DE).

(81) Designated States *(national)*: AU, BR, CA, CN, CZ, HU, IL, IN, JP, KR, MX, NZ, PL, RU, TR, US, ZA.

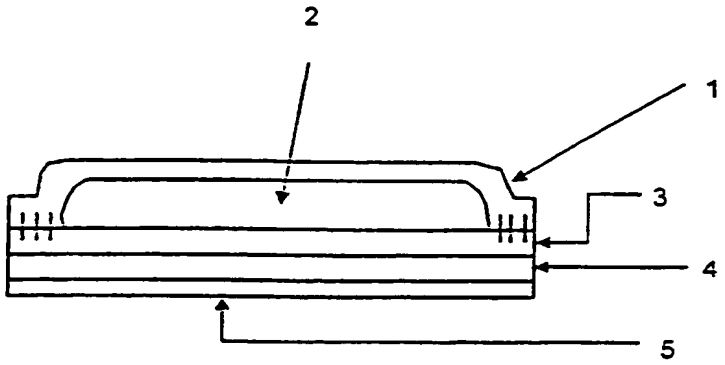
(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TRANSDERMAL THERAPEUTIC SYSTEM FOR ADMINISTERING A CALCIUM ANTAGONIST

schematic section of a TTS according to the invention



(57) Abstract: The invention relates to transdermal therapeutic systems for the therapeutic administration of calcium antagonists of the dihydropyridine type, to a process for its preparation and to its use in medicine.

WO 01/07017 A1

TRANSDERMAL THERAPEUTIC SYSTEM FOR ADMINISTERING A CALCIUM ANTAGONIST

Description

The present invention relates to a transdermal therapeutic system for the therapeutic administration of calcium antagonists of the dihydropyridine type, to a process for its preparation and to its use in medicine.

Calcium antagonists of the dihydropyridine type are compounds which influence the inflow of calcium ions into cells in particular into the cells of smooth muscles. Such compounds of the dihydropyridine type have been described, for example, in U.S. patent 3,799,934, U.S. patent 3,644,627, U.S. patent 4,264,611, and U.S. patent 4,801,599, which patents are incorporated by reference.

Calcium antagonists of the dihydropyridine type include, for example (without in any way limiting the scope of the invention), amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, and nitrendipine.

Diethyl (E)-4-[2-[(tert-butylcarbonyl)vinyl]phenyl-1,4-dihydro-2,6-dimethylpyridine-3,5 dicarboxylate (Lacidipine) is one of the preferred compounds of the dihydropyridine type. Lacidipine, which is described in British patent No. 2164336, is a potent long acting calcium antagonist which is particularly useful for treating hypertension. The compound may also be useful for the treatment of other cardiovascular disorders including atherosclerosis, peripheral vascular disease, ischaemic heart disease and congestive heart failure.

Nifedipine, which is described in U.S. patent 3,644,627, is another preferred calcium antagonists of the dihydropyridine type.

Transdermal drug delivery systems provide a means for obtaining a high degree of control of drug concentration in the blood over a specified time period. Many systems have been developed and used to deliver drugs transdermally. It is however widely recognised that in general it is not possible to predict which particular systems will

provide a satisfactory delivery system with a specific drug substance if that has not previously been adminstered by that route.

We have now found that calcium antagonists of the dihydropyridine type may be advantageously administered transdermally from a drug reservoir containing a solution comprising a calcium antagonist of the dihydropyridine type and at least one skin permeation enhancer.

Thus in one aspect the present invention provides a transdermal therapeutic system (hereinafter TTS) for administering calcium antagonists of the dihydropyridine type which comprises (a) a backing layer, which defines the upper surface of the device (b) a drug reservoir containing a solution comprising a calcium antagonist of the dihydropyridine type and at least one skin permeation enhancer, (c) a membrane to control the release of the active ingredient, (d) a pressure sensitive adhesive layer for attaching the system to the skin and, if necessary, a release liner on the outer face of the adhesive layer wherein the said backing layer and said membrane are connected together to form the drug reservoir.

In a further aspect the present invention provides for the use of calcium antagonists of the dihydropyridine type for the manufacture of a TTS for administration of calcium antagonists of the dihydropyridine type through a pre-determined area of intact skin for the treatment of cardiovascular disorders including hypertension.

In a preferred embodiment, the present invention provides a TTS for administering calcium antagonists of the dihydropyridine type, especially lacidipine or nifedipine, in the form of skin patch.

Figure 1 of the accompanying drawings gives a schematic section of a transdermal therapeutic system according to the invention.

Figure 2 of the accompanying drawings gives a top view of a transdermal therapeutic system according to the invention prior to fill and sealing.

For a therapeutic transdermal system according to the invention the backing layer (1) is preferably made of a sheet or a film of a flexible material that is substantially impermeable to the solution of the calcium antagonist of the dihydropyridine type. The layer is preferably of the order of 50 – 200 μm in thickness and may be optionally pigmented. Conveniently the backing layer (1) is heat sealable to the control membrane (3).

The layer (I) is preferably of a material that permits the device to follow the contours of the skin and be worn comfortably on areas of the skin such as joints of flexure. Examples of flexible polymers useful for the backing layer include polyethylene, polypropylene, polyesters and the like, which may be provided as films or laminates. A preferred flexible polymer is a laminate consisting of pigmented polyethylene aluminium vapour coated polyester and a medium density polyethylene or ethylene vinyl acetate heat seal layer available from 3M™ under the trade mark Scotchpack ™1006.

The solution comprising a calcium antagonist of the dihydropyridine type and at least one skin permeation enhancer may be in a liquid, semisolid or thixotropic form and is contained within the drug reservoir (2).

A suitable amount of a calcium antagonist of the dihydropyridine type present in the solution is within the range 1 – 20 % e.g. 1 - 10 % by weight of the total solution.

Examples of suitable solvents for preparing the solution of a calcium antagonist of the dihydropyridine type include an alkanol e.g. ethanol, propanol or isopropanol or N-methyl-2-pyrrolidinone or mixtures thereof e.g. ethanol and N-methyl-2-pyrrolidinone.

Example of suitable skin permeation enhancers of this invention include saturated and unsaturated fatty acid esters, alcohols such as ethanol, propanol, isopropanol, n-decyl alcohol, etc, pyrrolidone derivatives (i.e. N-methyl-2- pyrrolidone) or (+)1-methyl-4-(1-methylethenyl)cyclohexene: ((+) limonene).

Conveniently fatty acid ester enhancers include esters of carboxylic acids containing from C_8 to C_{16} carbon atoms. Preferred are those esters derived from palmitic acid, steric acid or lauric acid.

Conveniently fatty acid esters for use in the invention include fatty acid esters polyhydroxy alcohols such as sorbitol, glycerol or propylenglycol. Particularly preferred are fatty acids esters include those derived from sorbitol and of those sorbitan palmitate (Span™40) is particularly preferred.

Use of combinations of two or more of the skin permeation enhancer compounds may frequently result in superior results, such as greater transdermal absorption. Thus it has been found that a mixture of ethanol, N-methyl-2-pyrrolidone and sorbitan palmitate (Span™ 40) is a preferred skin permeation enhancing mixture.

The amount of ethanol present is conveniently within the range 10 - 60 % e.g. 30 - 40 % by weight of the total reservoir solution. The amount of Span™ 40 is conveniently within the range 0.5 - 6.0 % e.g. 1 - 5 % of the total reservoir solution. The amount of N-methyl-2-pyrrolidone present is conveniently within the range 20 - 70 % e.g. 40 - 70 % by weight of the total reservoir solution.

A particularly preferred reservoir solution of the invention contains 3 - 5 % e.g. 4 % of a calcium antagonist of the dihydropyridine type, such as lacidipine, 30 - 40 % e.g. 36.5 % of ethanol, 3 to 5 % e.g. 3.5 % of Span™ 40, and 50 - 60 % e.g. 56 % of N-methyl-2-pyrrolidone by weight of the total solution.

The solution comprising a calcium antagonist of the dihydropyridine type with one or more skin permeation enhancers forms a further aspect of the invention. This solution may be prepared by dissolving the calcium antagonist of the dihydropyridine type in a solution of the enhancers and the solvents using conventional procedures.

The membrane (3) to control the release of the calcium antagonist of the dihydropyridine type is a thin, flexible uniformly microporous, flat sheet membrane which provides a constant rate of drug release independent of time or of the amount of the active ingredient that remains in the reservoir. A preferred membrane is a flat

known under the Trade Mark Celgard™ 2400 or Celgard™ 2500, available from Hoechst Celanese. Celgard™ 2400 is the preferred membrane. Other suitable membranes include a microporus polyethylene membrane Solupor™ or an EVA membrane e.g. Co Tran™.

The contact adhesive layer (4) is a pressure-sensitive adhesive suitable for long term skin contact. It must also be physically and chemically compatible with the calcium antagonist of the dihydropyridine type and the vehicles employed. Further active ingredients must be soluble in the adhesive, so that the drug does not partition into the backing layer, but will partition into the skin. Conveniently the contact adhesive layer also adheres to the membrane (3).

Suitable adhesives include silicones, polyisobutylenes, polyacrilates, polyuretanes, plasticized ethylene, vinylacetate co-polymers, polystyrene-isoprene copolymer and a mixture thereof. Presently preferred contact adhesives are polyacrylates, silicones and polyurethanes.

Particularly preferred are the amine resistant silicone based pressure sensitive adhesives such as BIO-PSA Q7-4301, available from the Dow Corning Corp.

The release liner (5) is a disposable element which serves only to protect the adhesive layer prior to application to the skin. Typically, the release liner is formed from a material impermeable to the drug, vehicle, and adhesives and which is easily stripped from the contact adhesive.

Release liners are typically treated with silicone or fluorocarbons. A fluoro coated polyester film under the Trade Mark Scotchpatch™ 1022 available from 3M is particularly preferred.

In a further aspect of the invention provides a method for administering a calcium antagonist of the dihydropyridine type to a pre-determined area of intact skin, over defined time period and at an administration rate to reach and maintain an effective therapeutic dose of the calcium antagonist of the dihydropyridine type for the control

of hypertension and other cardiovascular diseases. In order to reach the effective blood levels of the drug a preferred rate of administration is between 0.1 to 2 μg/hr, more preferably in the range of 0.4 to 0.6 μg/hr, through a skin area of 2.0 to 90 cm^2, more preferably 10 to 40 cm^2. The amount of the drug delivered into the skin may be controlled by a number of factors, including skin patch size, degree of initial drug loading, the choice of skin permeation enhancers and the control release membrane.

The efficacy of the transdermal therapeutic system to deliver the calcium antagonist of the dihydropyridine type at the required rate and over the required time scale can be determined using conventional in vitro and in vivo test procedures. Thus for example using the in vitro procedure that is described by Franz J. T. Journal of Investigative Dermatology 64(3) 190 - 5 1975.

The present invention also provides a process for the production of the transdermal therapeutic system according to the invention which comprises the following steps:
a) coating the release liner (5) with the adhesive layer (4) which is then laminated with the control membrane (3);
b) securing the backing layer (1) to the control membrane (3) by means of a seal (7) so as to obtain the sachet (8) having an opening (6);
c) filling the reservoir (2) in the sachet (8) via the opening (6) with a solution comprising a calcium antagonist of the dihydropyridine type and at least one skin permeation enhancer and then sealing the opening (6);

In the preparation of the open reservoir sachet (8) it is convenient to use the backing layer (1) and the laminate comprising members (3), (4) and (5) in sheet form and when the said backing layer is sealed to the said laminate then the sachet (8) of the desired size and shape can be stamped or punched out either simultaneously with its formation or in a subsequent operation.

The individual TTS can be sealed into an appropriate packaging material using standard methods in the art. A convenient packaging material for use comprises a laminate of paper, polymer (i.e. polyethylene) and aluminium film. An example of a suitable means to seal the individual TTS into the appropriate packaging material is a

The example presented below serves to illustrate the invention without in any way limiting its scope:

Example 1

a) Preparation of the reservoir solution containing lacidipine – Dose per patch

N-methyl pyrrolidone(1.12 g) and sorbitan palmitate (Span™ 40) (0.07 g) were added to ethanol (0.737 g) and the solution obtained was stirred for about 30 min. Lacidipine (80 mg) was then added under stirring to obtain a homogeneous solution.

b) Preparation of the Transdermal Therapeutic System (TTS)

A solution of the silicone adhesive (4) [BIO-PSA Q7-4301: silicone resin, amine resistant, high tack 200 g/cm^2] was coated onto the release liner (5) [Scotchpak® 1022] . The control membrane (3) (Celgard® 2400) was then laminated to the dried adhesive layer. The backing layer (1) (Scotchpak® 1006) was then secured to the control membrane with a heat seal (7) to form a sachet (8) having a drug reservoir (2) connected to an opening (6). The drug reservoir (2) is then filled with the solution comprising lacidipine and at least one skin permeation enhancer via the opening (6) which is then heat sealed.

The patches of the following examples were prepared in an analogous manner

Example 2

Preparation of the reservoir solution containing nifedipine– Dose per patch

(+)-Limonene (0.37 g) was added to ethanol (1.60 g) and the solution obtained was stirred. Nifedipine (36 mg) was then added under stirring to obtain a homogeneous solution.

Example 3

Preparation of the reservoir solution containing nifedipine– Dose per patch

N-methyl pyrrolidone(1.12 g) and sorbitan palmitate (Span™ 40) (0.07 g) were added to ethanol (0.737 g) and the solution obtained was stirred for about 30 min. Nifedipine (82 mg) was then added under stirring to obtain a homogeneous solution.

Claims

1. A transdermal therapeutic system for administering a calcium antagonist of the dihydropyridine type which comprises (a) a backing layer, which defines the upper surface of the device, (b) a drug reservoir containing a solution comprising a calcium antagonist of the dihydropyridine type and at least one skin permeation enhancer, (c) a membrane to control the release of the active ingredient, (d) a pressure sensitive adhesive layer for attaching the system to the skin and, if necessary, a release liner on the outer face of the adhesive layer wherein the said backing layer and said membrane are connected together to form the drug reservoir.

2. A transdermal therapeutic system as claimed in claim 1 wherein the solution in the drug reservoir comprises a calcium antagonist of the dihydropyridine type, ethanol, N-methyl-2-pyrrolidinone and sorbitan palminate (Span™ 40).

3. A transdermal therapeutic system as claimed in claim 2 wherein the solution comprises a calcium antagonist of the dihydropyridine type 3 - 5 %, ethanol 30 - 40 %, sorbitan palmitate 3 - 5 % and N-methyl-2-pyrrolidinone 50 - 60 % by weight of the total solution.

4. A transdermal therapeutic system as claimed in any of claims 1 to 3 in the form of skin patch.

5. A transdermal therapeutic system as claimed in any of claims 1 to 4 in which the calcium antagonist of the dihydropyridine type is selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, and nitrendipine.

6. A transdermal therapeutic system as claimed in any of claims 1 to 5 in which the calcium antagonist of the dihydropyridine type is lacidipine.

7. A transdermal therapeutic system as claimed in any of claims 1 to 5 in which the calcium antagonist of the dihydropyridine type is nifedipine.

8. A transdermal therapeutic system essentially as described in the Examples.

9. The use of a calcium antagonist of the dihydropyridine type for the manufacture of a transdermal therapeutic system as claimed in any of claims 1 to 8 for administration of a calcium antagonist of the dihydropyridine type through a pre-determined area of intact skin for the treatment of cardiovascular disorders including hypertension.

10. A method for administering a calcium antagonist of the dihydropyridine type through a pre-determined area of intact skin and at an administration rate such as to reach and maintain an effective therapeutic dose of a calcium antagonist of the dihydropyridine type for the control of hypertension and other cardiovascular diseases which comprises applying to the skin a transdermal therapeutic system as claimed in any of claims 1 to 8.

11. A solution which is suitable for use in a transdermal therapeutic system as claimed in any of claims 1 to 8 which comprises a calcium antagonist of the dihydropyridine type and at least one skin permeation enhancer.

12. A solution as claimed in claim 11 which comprises a calcium antagonist of the dihydropyridine type, ethanol, N-methyl-2-pyrrolidinone and sorbitan palmitate.

13. A solution as claimed in claim 11 which comprises a calcium antagonist of the dihydropyridine type, ethanol and (+)-limonene.

14. A method of treating hypertension which comprises administering an effective amount of a calcium antagonist of the dihydropyridine type in a transdermal therapeutic system as claimed in any of claims 1 to 8.

Fig. 1: schematic section of a TTS according to the invention

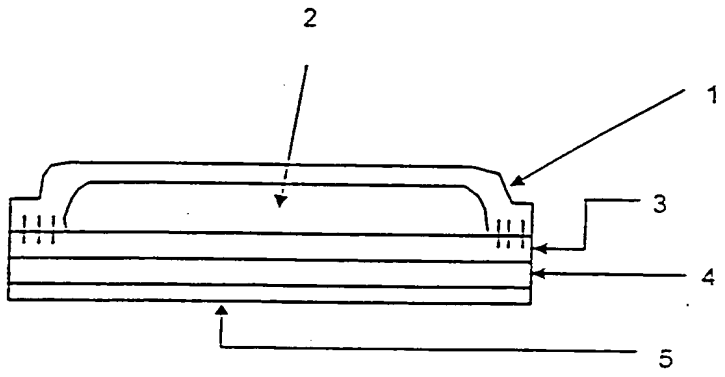
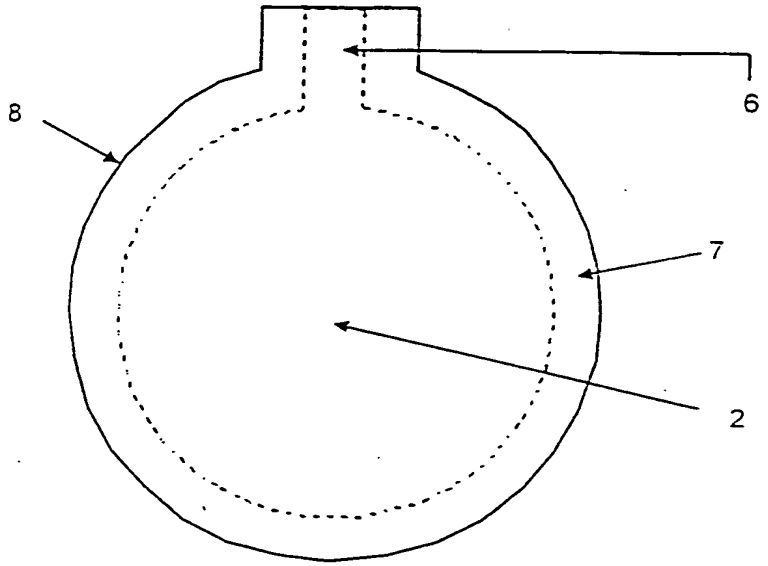


Fig. 2: top view of TTS according to the invention prior to filling and sealing



A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/70 A61K31/44 A61P9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 4 983 395 A (THERA_TECH INC.) 8 January 1991 (1991-01-08) column 3, line 17 -column 6, line 21 column 7, line 47 -column 8, line 2; example 3 claims 1-6	1,4,5, 8-11,14 13
A	& "Martindale 32th edition" , PHARMACEUTICAL PRESS , LONDON page 915, column 1 ---	9,10,14
X Y	US 4 956 171 A (CHANG YUNIK) 11 September 1990 (1990-09-11) column 3, line 14 - line 50 column 9; table 4 claims 1-6	1,4,5, 7-11,14 13
A	& "Martindale 32th edition" , PHARMACEUTICAL PRESS , LONDON page 919, column 3 --- -/--	9,10,14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 2000	11/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Muller, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 00/06215

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y A	EP 0 680 759 A (RHODE ISLAND EDUCATION) 8 November 1995 (1995-11-08) page 6 -page 7; examples 3,4 claims 1-11 & "Martindale 32th edition" , PHARMACEUTICAL PRESS , LONDON page 919, column 3	1,4,5, 7-11,14 13 9,10,14
Y	SHIRAKURA O; OHSHIMA A; TSUNEMI S: "Synergistic effect of D-Limonene and ethanol on the transdermal penetration of NB-818" DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, vol. 21, no. 4, 1995, pages 411-425, XP000961163 abstract	13
T	WO 00 47208 A (SEO BO YOUN ;CHO JOONG WOONG (KR); HWANG JUN SEOK (KR); SAMYANG CO) 17 August 2000 (2000-08-17) page 3, line 22 - line 24 page 6, line 22 -page 9, line 14 claims 1,2,15	2,3,12

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 8 relates to an extremely large number of possible systems. In fact, the term "essentially" in the claim contains so many options that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear, namely claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/EP 00/06215

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4983395 A	08-01-1991	US 4849224 A	18-07-1989
		AT 154751 T	15-07-1997
		AU 631417 B	26-11-1992
		AU 5341690 A	22-10-1990
		CA 2053272 A,C	22-09-1990
		DE 69030974 D	31-07-1997
		DE 69030974 T	18-12-1997
		DK 464106 T	21-07-1997
		EP 0464106 A	08-01-1992
		ES 2103271 T	16-09-1997
		HK 1003322 A	23-10-1998
		JP 8018976 B	28-02-1996
		JP 4506062 T	22-10-1992
		KR 149492 B	01-10-1998
		WO 9011065 A	04-10-1990
		AT 81023 T	15-10-1992
		AU 2467788 A	18-05-1989
		CA 1302824 A	09-06-1992
		DE 3875068 A	05-11-1992
		DE 3875068 T	15-04-1993
		EP 0316168 A	17-05-1989
		ES 2035928 T	01-05-1993
		GR 3006563 T	30-06-1993
		JP 1760026 C	20-05-1993
		JP 2001283 A	05-01-1990
		JP 4046592 B	30-07-1992
		KR 9301082 B	15-02-1993
US 4956171 A	11-09-1990	NONE	
EP 0680759 A	08-11-1995	NONE	
WO 0047208 A	17-08-2000	NONE	

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 00/06215

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/70 A61K31/44 A61P9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 4 983 395 A (THERA_TECH INC.) 8 January 1991 (1991-01-08) column 3, line 17 -column 6, line 21 column 7, line 47 -column 8, line 2; example 3 claims 1-6	1,4,5, 8-11,14 13
A	& "Martindale 32th edition" , PHARMACEUTICAL PRESS , LONDON page 915, column 1 ---	9,10,14
X Y	US 4 956 171 A (CHANG YUNIK) 11 September 1990 (1990-09-11) column 3, line 14 - line 50 column 9; table 4 claims 1-6	1,4,5, 7-11,14 13
A	& "Martindale 32th edition" , PHARMACEUTICAL PRESS , LONDON page 919, column 3 --- -/--	9,10,14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 2000	11/12/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Muller, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y A	EP 0 680 759 A (RHODE ISLAND EDUCATION) 8 November 1995 (1995-11-08) page 6 -page 7; examples 3,4 claims 1-11 & "Martindale 32th edition" , PHARMACEUTICAL PRESS , LONDON page 919, column 3	1,4,5, 7-11,14 13 9,10,14
Y	SHIRAKURA O; OHSHIMA A; TSUNEMI S: "Synergistic effect of D-Limonene and ethanol on the transdermal penetration of NB-818" DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, vol. 21, no. 4, 1995, pages 411-425, XP000961163 abstract	13
T	WO 00 47208 A (SEO BO YOUN ;CHO JOONG WOONG (KR); HWANG JUN SEOK (KR); SAMYANG CO) 17 August 2000 (2000-08-17) page 3, line 22 - line 24 page 6, line 22 -page 9, line 14 claims 1,2,15	2,3,12

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 8 relates to an extremely large number of possible systems. In fact, the term "essentially" in the claim contains so many options that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear, namely claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna[illegible] Application No
PCT/EP 00/06215

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4983395 A	08-01-1991	US 4849224 A	18-07-1989
		AT 154751 T	15-07-1997
		AU 631417 B	26-11-1992
		AU 5341690 A	22-10-1990
		CA 2053272 A,C	22-09-1990
		DE 69030974 D	31-07-1997
		DE 69030974 T	18-12-1997
		DK 464106 T	21-07-1997
		EP 0464106 A	08-01-1992
		ES 2103271 T	16-09-1997
		HK 1003322 A	23-10-1998
		JP 8018976 B	28-02-1996
		JP 4506062 T	22-10-1992
		KR 149492 B	01-10-1998
		WO 9011065 A	04-10-1990
		AT 81023 T	15-10-1992
		AU 2467788 A	18-05-1989
		CA 1302824 A	09-06-1992
		DE 3875068 A	05-11-1992
		DE 3875068 T	15-04-1993
		EP 0316168 A	17-05-1989
		ES 2035928 T	01-05-1993
		GR 3006563 T	30-06-1993
		JP 1760026 C	20-05-1993
		JP 2001283 A	05-01-1990
		JP 4046592 B	30-07-1992
		KR 9301082 B	15-02-1993
US 4956171 A	11-09-1990	NONE	
EP 0680759 A	08-11-1995	NONE	
WO 0047208 A	17-08-2000	NONE	

Rec'd PCT/PTO 17 JAN 2001
10/031529
WO 01/07017 PCT/EP00/06215

TRANSDERMAL THERAPEUTIC SYSTEM FOR ADMINISTERING A CALCIUM ANTAGONIST

Description

The present invention relates to a transdermal therapeutic system for the therapeutic administration of calcium antagonists of the dihydropyridine type, to a process for its preparation and to its use in medicine.

Calcium antagonists of the dihydropyridine type are compounds which influence the inflow of calcium ions into cells in particular into the cells of smooth muscles. Such compounds of the dihydropyridine type have been described, for example, in U.S. patent 3,799,934, U.S. patent 3,644,627, U.S. patent 4,264,611, and U.S. patent 4,801,599, which patents are incorporated by reference.

Calcium antagonists of the dihydropyridine type include, for example (without in any way limiting the scope of the invention), amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, and nitrendipine.

Diethyl (E)-4-[2-[(tert-butylcarbonyl)vinyl]phenyl-1,4-dihydro-2,6-dimethylpyridine-3,5 dicarboxylate (Lacidipine) is one of the preferred compounds of the dihydropyridine type. Lacidipine, which is described in British patent No. 2164336, is a potent long acting calcium antagonist which is particularly useful for treating hypertension. The compound may also be useful for the treatment of other cardiovascular disorders including atherosclerosis, peripheral vascular disease, ischaemic heart disease and congestive heart failure.

Nifedipine, which is described in U.S. patent 3,644,627, is another preferred calcium antagonists of the dihydropyridine type.

Transdermal drug delivery systems provide a means for obtaining a high degree of control of drug concentration in the blood over a specified time period. Many systems have been developed and used to deliver drugs transdermally. It is however widely recognised that in general it is not possible to predict which particular systems will

Claims

1. A transdermal therapeutic system for administering a calcium antagonist of the dihydropyridine type which comprises (a) a backing layer, which defines the upper surface of the device, (b) a drug reservoir containing a solution comprising a calcium antagonist of the dihydropyridine type and at least one skin permeation enhancer, (c) a membrane to control the release of the active ingredient, (d) a pressure sensitive adhesive layer for attaching the system to the skin and, if necessary, a release liner on the outer face of the adhesive layer wherein the said backing layer and said membrane are connected together to form the drug reservoir.

2. A transdermal therapeutic system as claimed in claim 1 wherein the solution in the drug reservoir comprises a calcium antagonist of the dihydropyridine type, ethanol, N-methyl-2-pyrrolidinone and sorbitan palminate (Span™ 40).

3. A transdermal therapeutic system as claimed in claim 2 wherein the solution comprises a calcium antagonist of the dihydropyridine type 3 - 5 %, ethanol 30 - 40 %, sorbitan palmitate 3 - 5 % and N-methyl-2-pyrrolidinone 50 - 60 % by weight of the total solution.

4. A transdermal therapeutic system as claimed in any of claims 1 to 3 in the form of skin patch.

5. A transdermal therapeutic system as claimed in any of claims 1 to 4 in which the calcium antagonist of the dihydropyridine type is selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, and nitrendipine.

6. A transdermal therapeutic system as claimed in any of claims 1 to 5 in which the calcium antagonist of the dihydropyridine type is lacidipine.

7. A transdermal therapeutic system as claimed in any of claims 1 to 5 in which the calcium antagonist of the dihydropyridine type is nifedipine.

8. A transdermal therapeutic system essentially as described in the Examples.

9. The use of a calcium antagonist of the dihydropyridine type for the manufacture of a transdermal therapeutic system as claimed in any of claims 1 to 8 for administration of a calcium antagonist of the dihydropyridine type through a pre-determined area of intact skin for the treatment of cardiovascular disorders including hypertension.

10. A method for administering a calcium antagonist of the dihydropyridine type through a pre-determined area of intact skin and at an administration rate such as to reach and maintain an effective therapeutic dose of a calcium antagonist of the dihydropyridine type for the control of hypertension and other cardiovascular diseases which comprises applying to the skin a transdermal therapeutic system as claimed in any of claims 1 to 8.

11. A solution which is suitable for use in a transdermal therapeutic system as claimed in any of claims 1 to 8 which comprises a calcium antagonist of the dihydropyridine type and at least one skin permeation enhancer.

12. A solution as claimed in claim 11 which comprises a calcium antagonist of the dihydropyridine type, ethanol, N-methyl-2-pyrrolidinone and sorbitan palmitate.

13. A solution as claimed in claim 11 which comprises a calcium antagonist of the dihydropyridine type, ethanol and (+)-limonene.

14. A method of treating hypertension which comprises administering an effective amount of a calcium antagonist of the dihydropyridine type in a transdermal therapeutic system as claimed in any of claims 1 to 8.